A New Antihypertensive Agent

Clinical Evaluation of a Rauwolfia-Flumethiazide Combination (Rautrax®)

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• **Twenty-eight patients were treated with Rautrax,® a combination of flumethiazide, rauwolfia and potassium chloride for from one to seven months. The average mean blood pressure for the group declined from 135 mm. of mercury to 107 mm. All but two of the patients had a decrease in blood pressure and 19 became normotensive. Associated symptoms of headache, dyspnea, edema and angina were completely relieved or improved in the majority of patients with these complaints. On the basis of the blood pressure response and the clinical effects seen in the patient, therapeutic results were classified as good to excellent in 22 of the 28 patients, fair in two, and poor in three. No evaluation was made in the remaining patient in the series because further adjustment in dosage was required.**

Three patients had side effects—moderate gastrointestinal upset in one case, headache and a sensation of the bladder's having been "wrung out" in another, and headache and paresthesia of the legs in the third. Only the third patient had persisting symptoms after the drug was discontinued. In the other two reduction of dosage sufficed.

THE USEFULNESS of chlorothiazide and similar compounds as adjuncts to other antihypertensive therapy has gained increasing recognition within recent years.[1,2,4,6,7] Since the effectiveness of antihypertensive agents generally is enhanced by using diuretic-saluretic preparations with them, the hazard of side effects can be lessened by reducing the dose without sacrifice of therapeutic effect. However, electrolyte disturbance may accompany active diuresis and some difficulty from potassium loss from use of these adjunctive drugs has been reported.[5]

Recently a new preparation, Rautrax,® which is designed especially to provide antihypertensive therapy without the problem of potassium loss, has become available for clinical use. It combines the well-recognized antihypertensive agent rauwolfia serpentina (whole root) with a new oral diuretic agent, flumethiazide, with added potassium chloride. I used Rautrax® over a period of seven months in the treatment of unselected hypertensive patients and found it remarkably effective, especially in patients with essential hypertension.

Eight men and 20 women were treated. The range of ages was from 44 to 80 years, 18 patients being 60 years old or older. Hypertension was noted on routine physical examination in all cases. "Essential" hypertension was the diagnosis in 22 cases, hypertension associated with arteriosclerosis in four others. In the remaining two the disease was classified as combined essential and arteriosclerotic hypertension. The range of blood pressure was from 150 to 245 mm. of mercury systolic, and from 95 to 135 mm. diastolic, with an average for the series of approximately 192/106 mm.

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Associated conditions noted on examination of the patients or derived from the history included the following:

Condition	Present	Past	No. of Patients
Arteriosclerosis	x		8
Cerebrovascular accident		x	2
Heart disease	x		5
Cardiac infarction		x	2
Angina pectoris	x		3
Cerebral dysrythmia	x		1
Arthritis	x		1
Osteoporosis	x		2
Obesity	x		6
Menopause	x		4
Allergy	x		3
Carcinoma of bladder	x		1
Cholelithiasis	x		1
Parkinson's disease	x		1
Hypothyroidism	x		1

In a number of cases, more than one of the conditions given in the table were present in the same patient.

Two additional patients were originally included in the series but were dropped from the study before evaluation of results could be made. One of these patients died suddenly after approximately a month of treatment. She had appeared to be well the day before she died. Even so, her death was not unexpected, for she had a history of long-standing hypertension with associated angina and on one occasion had had some cardiac decompensation. The other patient was dropped from the study because gastrointestinal upsets developed after almost a month of therapy with Rautrax® and the drug had to be discontinued. She had had similar reactions previously with other rauwolfia preparations.

TABLE 1.—*Blood Pressure Response to Rautrax® in 28 Hypertensive Patients*

	No. of Patients Treated	Average Mean Blood Pressure (mm. Hg.)* Initial	Posttherapy	No. Becoming† Normotensive	No. with Drop in Mean Blood Pressure of at Least 20 mm. of Mercury
Men	8	138	103	6	8
Women	20	133	111	13	10
Entire series	28	135	107	19	18

*Mean blood pressure: Diastolic plus one third of pulse pressure.
†Normotensive: Mean blood pressure of 110 mm. of mercury or less.

TABLE 2.—*Evaluation of Clinical Response to Rautrax® in 28 Hypertensive Patients*

Clinical Response	No. of Patients Male	Female	Total
Excellent	5	11	16
Good	2	4	6
Fair	1	1	2
Poor	0	3	3
No elevation	0	1*	1
Totals	8	20	28

*Pronounced decrease in blood pressure obtained with 1 tablet of medication three times a day was followed by rise when dosage was reduced to 1 tablet daily. Dosage was not yet adjusted at time of report.

Rautrax® contains in each tablet 50 mg. of whole root rauwolfia serpentina, 400 mg. of flumethiazide and 400 mg. of potassium chloride. The action of whole root rauwolfia in lowering the blood pressure and relieving associated "hypertensive" symptoms is well recognized. Flumethiazide is a new oral nonmercurial drug with diuretic activity roughly equivalent to that of chlorothiazide, to which tolerance does not develop.[3] Although a saluretic agent, flumethiazide does not significantly alter the concentrations of serum electrolytes.[3] Moyer said that flumethiazide has less effect on potassium excretion than do chlorothiazide and hydrochlorothiazide.[5] Potassium chloride was added as an ingredient of Rautrax® to protect against any loss of potassium that might occur from the saluretic action of the drug.

At the beginning of treatment the dose of Rautrax® was one tablet three or four times a day. Usually the dosage was reduced later to one or two tablets daily, depending upon the clinical response of the patient, but seven patients continued to receive the initial amount throughout the period of treatment. At the time of this report, the patients had been treated for from one to seven months, half of them for at least five months.

RESULTS

The therapeutic results obtained in this series are categorized in Tables 1 and 2. Clinical results were very satisfactory in the majority of patients. The average mean blood pressure* for the group as a whole decreased from the initial level of 135 mm. of mercury to 107 mm. Blood pressure levels declined in all but two of the 28 patients, significantly so in 18,† and reached normal levels‡ in 19 patients (Table 2). Although proportionally more men than women became normotensive, the difference probably was related to the presence or absence of sclerosis rather than the sex of the patient.

Associated symptoms of headache, dyspnea, edema and angina were completely relieved or improved in the majority of patients who had them. One patient with arteriosclerotic heart disease associated with hypertension was able to discontinue the use of digitalis and of additional diuretics while receiving Rautrax.® She had not been able to do so with previous antihypertensive therapy. A patient who had cerebral dysrhythmia in addition to the hypertension had no major attacks of unconsciousness and less frequent episodes of myoclonia and visual disturbances after treatment with Rautrax.®

On the basis of the observed decrease in blood pressure to normal or near normal levels and the clinical improvement in most or all of the associated symptoms, therapeutic results were considered to be excellent in 16 patients, good in six and fair in two.

In three other patients, there was little or no improvement either in blood pressure or in the relief of symptoms, and the results of treatment were rated as poor. No evaluation was made in the remaining patient in the series because the dosage had not been effectively stabilized at the time of report. Although her blood pressure decreased from 170/110 to 125/85 mm. of mercury with the initial dosage (one tablet three times a day) it rose to 160/100 mm. when the dose was reduced to one tablet a day, and further adjustment in dosage of the drug was indicated.

Side effects were observed in only three patients. One had moderate gastrointestinal upset while taking four tablets daily, but not after the dosage was reduced to three tablets a day. In another case Rautrax® was discontinued when the patient complained of a peculiar headache and paresthesia of the legs. Reducing the dosage did not relieve these symptoms and they persisted for two months after the drug was discontinued. This patient had generalized arteriosclerosis with severe hypertension and had had a "stroke" three years before. One possible explanation is that these symptoms may have been a reaction of the central nervous system to the dehydration induced by the drug. A patient who had habitually complained of side effects from

* Mean blood pressure is defined here as diastolic pressure plus one-third of pulse pressure.
† Drop in mean blood pressure of at least 20 mm. Hg.
‡ Mean blood pressure of 110 mm. Hg. or less.

previous medication, said she had severe headache while taking three tablets of Rautrax® a day. On her own initiative she stopped taking it. Then when she resumed the drug at 1 tablet daily, under medical direction, she felt better; but when the dosage was increased again to three tablets a day she complained that her bladder felt "wrung out."

One of the men died during treatment but his death was not unexpected since he had coronary arteriosclerosis with angina and had had coronary occlusion some years before. In this patient a massive anterior cardiac infarction occurred some two months after the blood pressure had decreased under treatment with Rautrax® from 180/110 to 120/70 mm. of mercury. He died 11 days later, probably of ventricular fibrillation.

The general impression of Rautrax® from this trial was that it is a remarkably effective material and a valuable antihypertensive agent at least for the initial phase of treatment of patients with essential hypertension.

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